ZOOLOGY.—*Resistance of rats to superinfections with a nematode,* Nippostrongylus muris, *and an apparently similar resistance of horses to superinfection with nematodes.*[1] BENJAMIN SCHWARTZ, JOSEPH E. ALICATA and JOHN T. LUCKER, Bureau of Animal Industry, U. S. Department of Agriculture.

For the past twenty-five years parasitologists have been seeking evidence in regard to immunity in parasitic infections. By means of the known immunological technic developed in connection with the study of bacterial and related diseases, it has been possible to demonstrate more or less specific antibodies in certain diseases caused by metazoan parasites, particularly in schistosomiasis, hydatid disease, trichinosis, filariasis, and some of the worm infestations of the gastro-intestinal tract of various mammals. While the evidence obtained in the course of these investigations is of interest and of value, and shows that certain substances eliminated by the parasites involved are probably absorbed by the host with the resultant elaboration of antibodies, it falls short of explaining how the host actually copes with the parasites themselves, particularly in cases of superinfections. More recently a number of parasitologists have presented data, based on laboratory investigations, which appear to indicate that following the successive administration of infective nematode larvae to susceptible host animals, the latter ultimately become entirely refractory, or nearly so, to an infection with the particular parasites involved. The evidence presented in connection with the latter investigations has been in the main indirect, and has been based, for the most part, on information derived from quantitative studies in the form of counts, made at regular intervals of the number of worm eggs in definite amounts of the feces of experimentally infected animals, the rise and fall in the intensity of the parasitic infestations being judged by the relative number of parasite eggs present in definite quantities of feces. In the opinion of the present writers, however, evidence of this sort has definite usefulness and value, and also definite limitations. It fails to give an accurate index to the total number of worms harbored by a host, since the evidence of egg counts takes cognizance only of female worms which have attained fertile maturity, and gives no direct or positive information in regard to males, immature worms, or senile females, which might be present in the host in considerable numbers. This limitation has been pointed out from time to time in the past, but even yet is not always taken into consideration or kept in mind. The significance

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of the possible presence of agamic parasites in a state of arrested development has been entirely overlooked in the past.

The writers' investigations on the life history of *Nippostrongylus muris*, a nematode parasitic in the small intestine of rats, and more or less closely related to pathogenic trichostrongyles occurring in domestic meat-food animals, have already brought to light facts which show rather conclusively that following the recovery from a single infection with this nematode, under rigorous experimental conditions which have precluded extraneous infections with this and with other parasites, the rat host is already in a state of relative resistance to superinfection. If exposed to a second infection or to subsequent infections, the development of the parasites is considerably retarded, but agamic worms commonly remain in the host and may ultimately come to fertile maturity, apparently a few at a time.

As first shown by Yokagawa in 1925, the infective larvae of *Nippostrongylus muris* may enter the host through the skin and be carried by the circulation to the lungs. In these organs the larvae develop for a time and then migrate to the small intestine in a manner similar to that of various species of human and carnivore hookworms, species of ascarids, and other intestinal parasites which undergo part of their development in the lungs. In about six to seven days after experimental infection with *N. muris*, the worm eggs appear in the feces of infested rats. The writers' investigations have shown that once the the eggs have appeared in the feces, their production, as followed by microscopic examination of the feces, rises rather rapidly at first, then declines gradually, and finally the eggs disappear from the feces altogether. Experimentally infected rats, killed from 13 to 16 days following infection, and about 7 to 10 days after the first appearance of eggs in the feces, contained fully grown, sexually mature worms, the females being, as a rule, at the peak of egg production, but sometimes already on the decline in production. Occasionally a few larvae, usually from three to five, have been discovered in the lungs of such rats. These larvae are worms which, for one reason or another, have failed to get into the intestine and have, therefore, been unable to develop beyond the stage which these parasites can attain in the lungs.

In experimental rats killed from 13 to 16 days following the first superinfection, subsequent to the disappearance from the feces of eggs resulting from the previous infection, the parasite picture discovered at necropsy was quite different from that noted at the corresponding stage in the course of the first infection. In some rats many of the worms from the second infection, in some cases 50 per cent or more, were still in the lungs as third-stage larvae; the worms recovered from the intestine were, for the most part, not fully grown and many of the females had not yet attained the egg-laying stage. Before being killed, the rats in question showed an insignificant number of eggs in the feces as compared to the large number of eggs present at a corresponding stage of development in the first infection. At necropsy, the egg-producing females from the second infection were found to contain relatively few eggs in the uterus.

While direct evidence based on the finding of worms post-mortem, about two weeks after a second or a third superinfection of rats, is as yet unavailable, indirect evidence, based on the period required for eggs to appear in the feces following such successive infections, indicates that the prepatent period increases directly with the number of times that these host animals are exposed to re-infection. This is interpreted as indicating that with successive infections the host builds up an increasing resistance of a sort resulting in retardation of the growth and the development of these nematodes, possibly by elaborating, either throughout the body or, what is, perhaps, more probable, in the tissues and organs with which these worms come in contact, a specific growth-inhibiting substance or substances which retard the development of the parasites. So far as the writers are aware, this is the first experimental demonstration of what appears to be the development by the host of a growth-inhibiting mechanism for keeping in check the development and propagation of a parasitic nematode.

In connection with an investigation on the prevalence in horses of species of *Habronema,* heteroxeneous nematodes which are transmitted by flies, it was discovered that despite the absence of flies during the the winter months in the vicinity of the District of Columbia, agamic forms of *Habronema* species, in many cases no further advanced in development than that attained in their intermediate fly hosts, were present in the stomachs of horses during the months of December, 1930, to March, 1931 inclusive.[2] In the light of the experimental results obtained with *N. muris,* the writers interpret these findings in horses as probably falling within the same category of resistance as that discovered in connection with the superinfection experiments with the rat trichostrongyle discussed in this paper. It is not improbable that in cases of superinfections with other species of nematodes a growth-retarding mechanism, similar to that discovered in rats infected with *Nippostrongylus muris,* will be found.

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[2] These data were collected by Mr. Allan McIntosh, Assistant Zoologist, Bureau of Animal Industry.